25. (Added) The method of claim 21 wherein the antigen is derived from any of Human Immunodeficiency Virus, Feline Immunodeficiency Virus, Herpes Simplex Virus type 1, Herpes Simplex virus type 2, Human cytomegalovirus, Hepatitis A, B, C or E, Respiratory Syncytial virus, human papilloma virus, Influenza virus, Salmonella, Neisseria, Borrelia, Chlamydia, Bordetella, Plasmodium and Toxoplasma.

26. (Added) The method of claim 21 wherein the antigen is a tumor antigen.

27. (Added) The method of claim 21 wherein a cytolytic T cell response to the antigen is induced.

28. (Added) The method of claim 21 wherein interferon γ production is stimulated.

29. (Added) The method of claim 21 wherein the QS21 and 3D-MPL synergistically enhance the immune response.

Remarks

The above amendments are believed to place this application in condition for allowance or, in any event, to put this application in better condition for appeal. No new subject matter is added or claimed. Therefore, entry of these amendments is respectfully requested.

Claims 1, 3, 12 and 15 are amended to delete the reference to "antigenic compositions" and "combinations." Upon further reflection of the Examiner's earlier objection to these terms, Applicants now believe that these terms in the claims are unnecessary and are potentially confusing. Instead, the claims now recite only the term, "antigen," because this term is broad enough to encompass "antigenic compositions" as well as "combinations" of antigens and of antigenic compositions.

Claims 21-29 are directed to methods of enhancing the immune response in an animal to an antigen or antigens. These claims are supported throughout the specification. It is clear from the specification that enhancing the immune response means increasing the immune response over what it would have been in the absence of the QS21 and 3D-MPL, *e.g.*, by increasing the CTL response, by stimulating interferon γ production, by increasing an antibody response, *etc.* The

claims present no new subject matter or new issues of patentability and do not require additional searching. Therefore, entry of these claims is respectfully requested.

Applicants submit the following remarks with respect to the grounds of rejection.

Double Patenting.

One of the applications over which this rejection was made has been abandoned. The claims in this case, and in the co-pending case over which this application has been rejected for double patenting, will be amended following receipt of an indication of allowability. Applicants appreciate the Examiner's prior acknowledgment of this.

Rejection of claim 6 under 35 U.S.C. 112, first paragraph

Applicants canceled claims 6 and 13 because they are superfluous in view of claim 1, on which claims 6 and 13 depended, and in view of other of the remaining claims that are not limited to specified antigens. In addition, as noted above, Applicants are pursuing claims that relate to the vaccine composition of the invention wherein the antigen is a HSV antigen in a co-pending application because such vaccine is presently in clinical development and is of particular commercial importance to Applicants.

Moreover, Applicants have added claim 25 which specifically recites a method of enhancing the immune response in an animal to antigens derived from the various pathogens previously recited in claim 6. Applicants respectfully submit that the reasons for rejecting claim 6 under 35 USC 112, first paragraph, do not apply to claim 25 because claim 25 is directed merely to a method of enhancing the immune response to a given antigen.

The specification supports enhancement of an immune response to a HIV antigen. In any event, Applicants herewith submit, in unsigned form, a declaration by Dr. Garcon, one of the inventors. That declaration, a signed copy of which will be submitted shortly, demonstrates, in Paragraph 5 (results shown in Table 2), that the combination of QS21 and 3D-MPL enhances the immune response to HIV gp120.

The rejection of claim 6 is apparently predicated on an alleged lack of correlation between in vitro and in vivo effects of immunizing against HIV. However, this lack of correlation between in vivo effects and in vitro effects, as explained by the Examiner, relates to the effectiveness of an immune response in

treating or preventing disease. Claim 25 does not recite or even imply prevention of cure of any given disease.

Prior Art Rejections

Although the Examiner has criticized Applicants' previous arguments for failing to address the collective teachings of the references, the fact remains that the Examiner has not shown any teaching or suggestion in the references, taken singly or in combination, or given any reason to persons of ordinary skill in the art, to select the particular combination of adjuvants (QS21 and 3D-MPL) discovered by Applicants.

Looking first at the references individually, Kensil et al., at column 7, lines 14-40, mentions various saponins that can be combined with various other adjuvants but do not mention QS21 or 3D-MPL. Similarly, Schneerson et al. and Cantrell both teach combinations of MPL with various other adjuvants, e.g., oil-in-water, liposomes, and microbial cell wall skeleton, but does not suggest combinations of QS21 with 3D-MPL. (Long et al. does not teach or suggest adjuvant combinations.)

Taken collectively, the references teach various combinations of adjuvants but do not teach or suggest the particular combination of QS21 and 3D-MPL. It is only with hindsight that these two adjuvants in particular can be selected to make an adjuvant composition.

In addition, the Examiner does not seem to have taken account of the unexpected beneficial effects that can be provided by the combination of QS21 plus 3d-MPL. Yet, the specification discloses unexpected synergies and improvement in certain immune responses when these two adjuvants are combined. For example, in Example 1, Applicants demonstrated unexpected synergy resulting in enhanced gamma-interferon induction upon administration of QS21 and 3D-MPL with a herpes virus antigen. In Example 2, Applicants demonstrated unexpected synergy resulting in an enhanced CTL response upon administration of QS21 and 3D-MPL with a malaria sporozoite antigen.

Furthermore, the Garcon Declaration provides additional data showing unexpected enhancement of the immune response with various antigens. Specifically,

- paragraph 3, (Figure 1) shows a synergistic increase in antibody titers to a HBV antigen when QS21 is combined with 3D-MPL compared with either QS21 or 3D-MPL alone;

- paragraph 4 (Table 1) shows an enhanced IgG2a response to an HBV antigen when 3D-MPL is combined with QS21 compared with alum alone and also compared with the combination of alum and 3D-MPL;
- paragraph 5 (Table 2) shows that the combination of QS21 and 3D-MPL unexpectedly enhances gamma-interferon and IL-2 production following administration of a HIV antigen;
- paragraph 6 (Tables 3 and 4), shows that the combination of QS21 and 3D-MPL unexpectedly enhances antibody titers to a RSV antigen (Table 3) the stimulation index (CMI) following administration of a RSV antigen (Table 4).

These data, along with the data presented in the specification, demonstrate that the adjuvant formulation of the invention can result in unexpected, and in some cases synergistic, enhancement of the immune response. In other experiments, results not shown, Applicants demonstrated that the QS21/3D-MPL adjuvant enhanced the therapeutic effect of a vaccine containing HSV gD antigen; prophylaxis with the same antigen and adjuvant combination was also shown although there was no apparent enhancement in the prophylactic effect.

Finally, Applicants note that in spite of the advances in adjuvant technology that have been made, as evidenced by the references of record, there remains a long-felt need for improved vaccine adjuvants. Applicants have helped to satisfy this need with their important discovery.

In view of the above amendments and remarks, which Applicants believe are fully responsive to the outstanding office action, Applicant respectfully request reconsideration of the rejections of the claims. The Examiner is invited to

contact Applicants' undersigned attorney at the number provided below if this might facilitate prosecution of this case.

Respectfully submitted,

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